

T06050-95215360

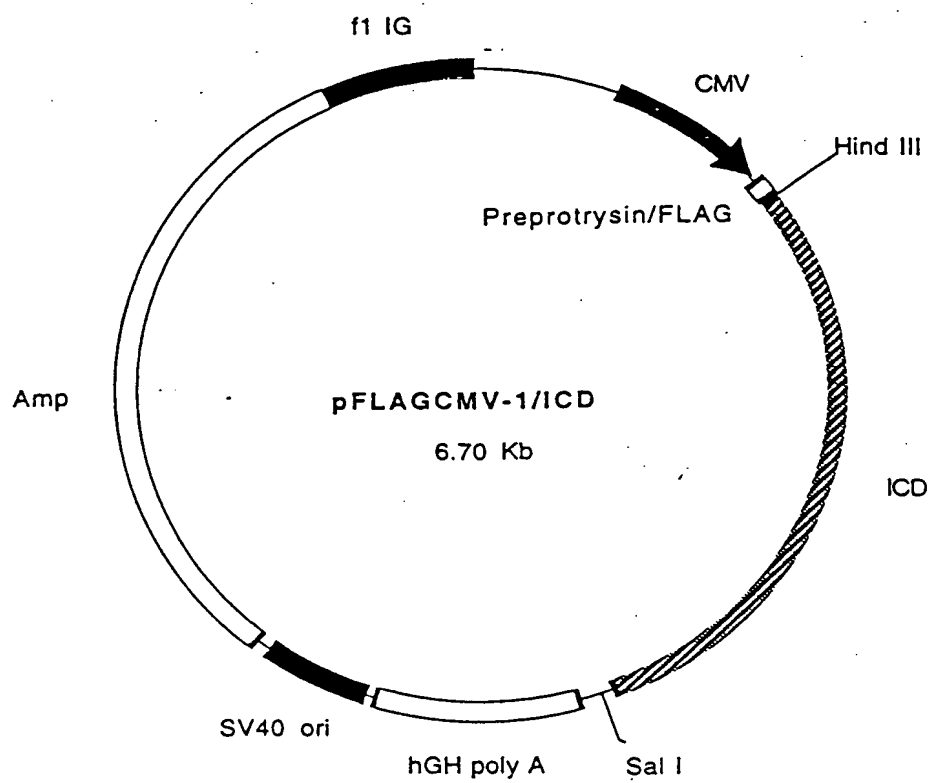


Fig. 1

106050-95E15860

Fig. 2

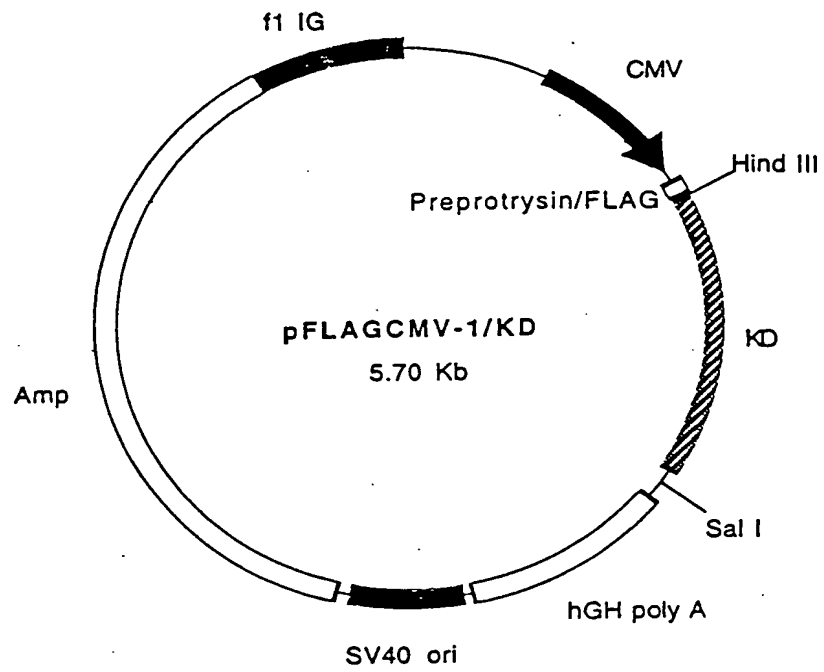


Fig. 3

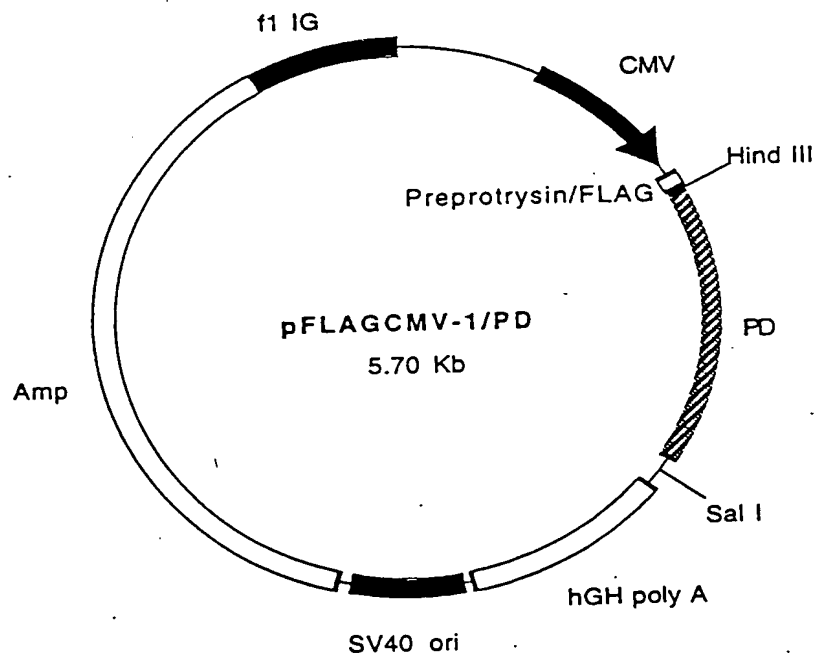
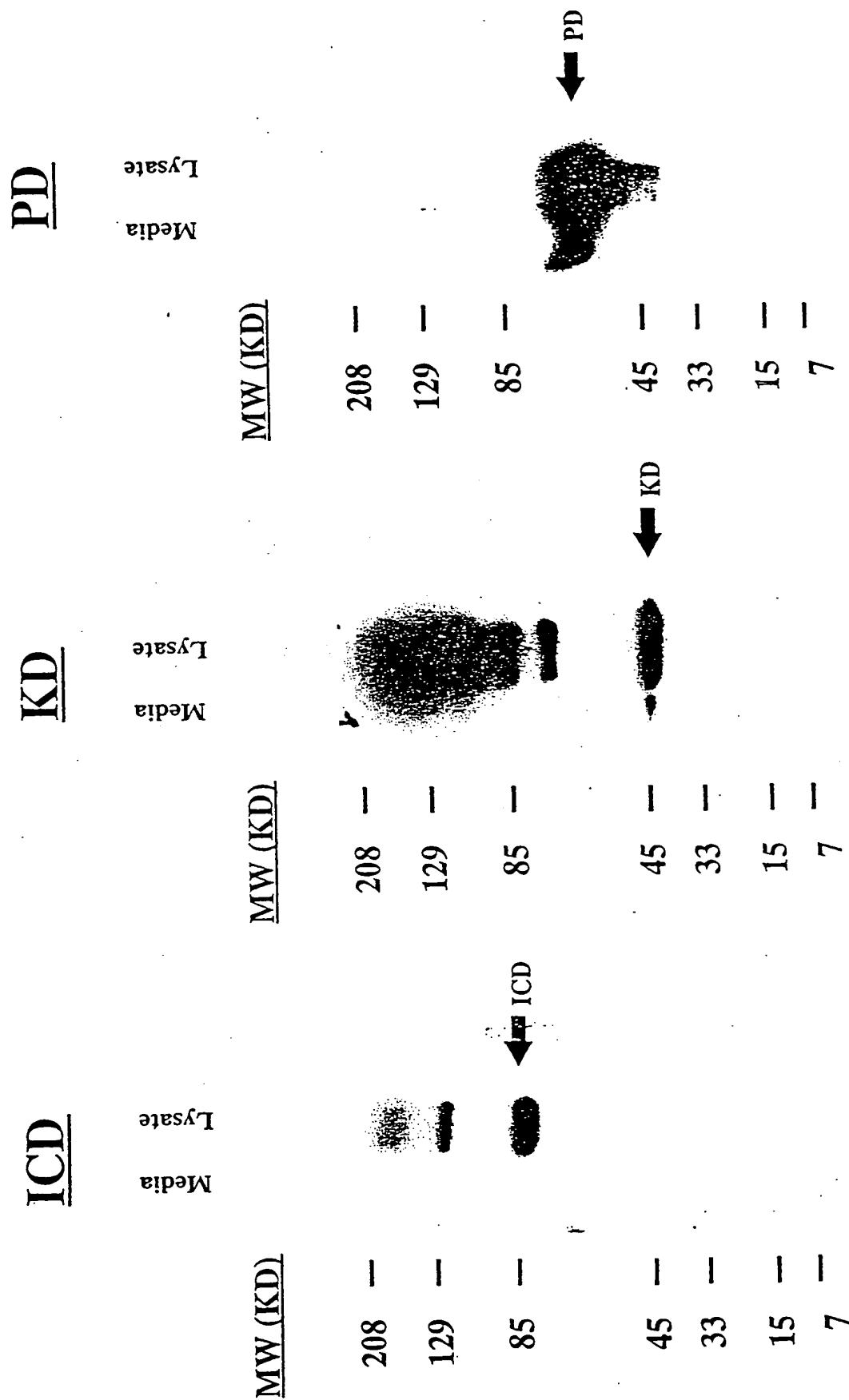


Fig. 4



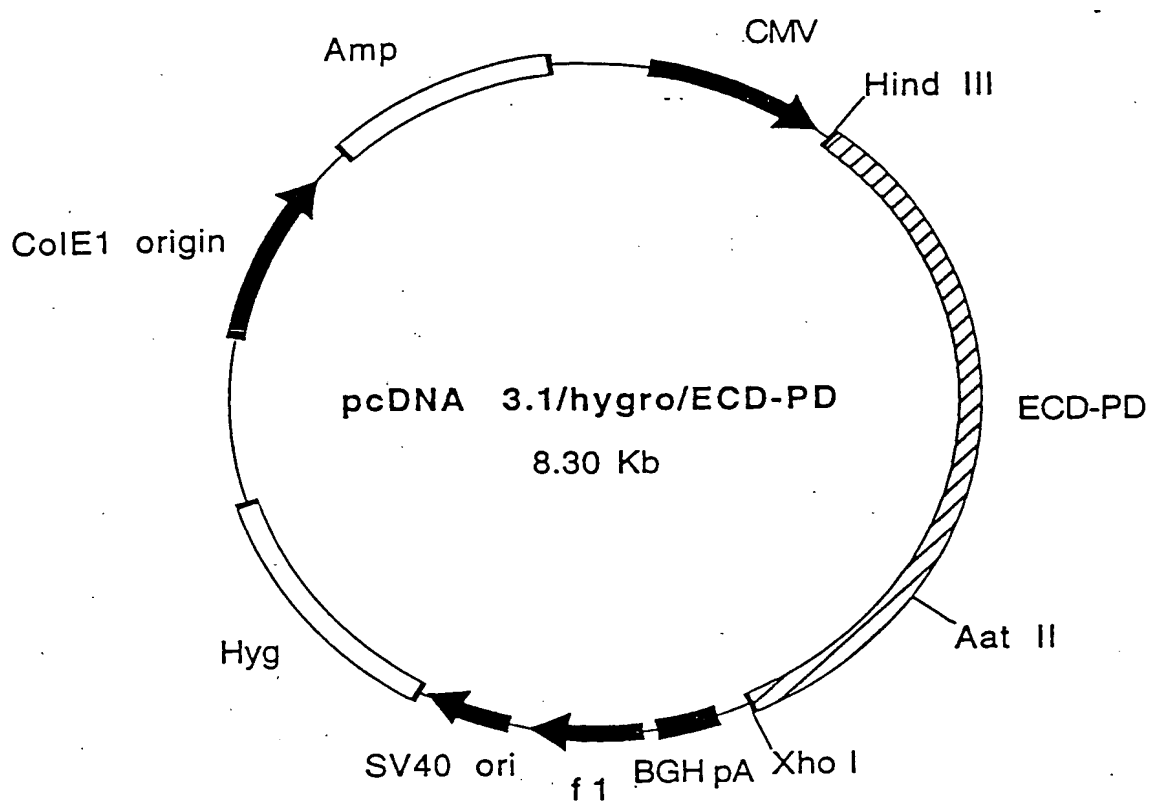


Fig. 5

# pcDNA3.1hyg/ECD-PD expression

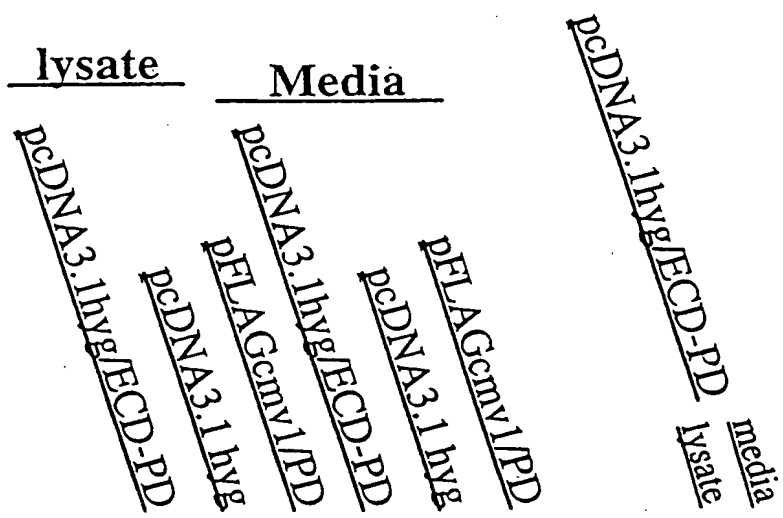


Fig. 6A



Fig. 6B

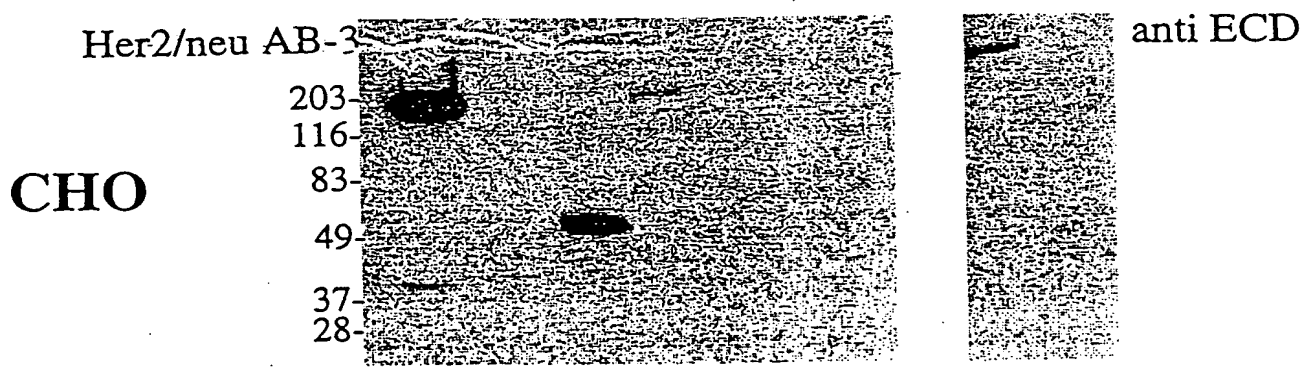


Fig. 7 (SEQ ID NO: 1)

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|-----|
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 10  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 20  |
| Met | Glu | Leu | Ala | Ala | Leu | Cys | Arg | Trp | Gly | Leu | Leu | Leu | Ala | Leu | Leu | Pro | Pro | Gly | Ala | 20  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Ser | Thr | Gln | Val | Cys | Thr | Gly | Thr | Asp | Met | Lys | Leu | Arg | Leu | Pro | Ala | Ser | Pro | Glu | 40  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Thr | His | Leu | Asp | Met | Leu | Arg | His | Leu | Tyr | Gln | Gly | Cys | Gln | Val | Val | Gln | Gly | Asn | Leu | 60  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Glu | Leu | Thr | Tyr | Leu | Pro | Thr | Asn | Ala | Ser | Leu | Ser | Phe | Leu | Gln | Asp | Ile | Gln | Glu | Val | 80  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Gln | Gly | Tyr | Val | Leu | Ile | Ala | His | Asn | Gln | Val | Arg | Gln | Val | Pro | Leu | Gln | Arg | Leu | Arg | 100 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 110 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 120 |
| Ile | Val | Arg | Gly | Thr | Gln | Leu | Phe | Glu | Asp | Asn | Tyr | Ala | Leu | Ala | Val | Leu | Asp | Asn | Gly | 120 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Asp | Pro | Leu | Asn | Asn | Thr | Thr | Pro | Val | Thr | Gly | Ala | Ser | Pro | Gly | Gly | Leu | Arg | Glu | Leu | 140 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Gln | Leu | Arg | Ser | Leu | Thr | Glu | Ile | Leu | Lys | Gly | Gly | Val | Leu | Ile | Gln | Arg | Asn | Pro | Gln | 160 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Cys | Tyr | Gln | Asp | Thr | Ile | Leu | Trp | Lys | Asp | Ile | Phe | His | Lys | Asn | Asn | Gln | Leu | Ala | 180 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Thr | Leu | Ile | Asp | Thr | Asn | Arg | Ser | Arg | Ala | Cys | His | Pro | Cys | Ser | Pro | Met | Cys | Lys | 200 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 210 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 220 |
| Gly | Ser | Arg | Cys | Trp | Gly | Glu | Ser | Ser | Glu | Asp | Cys | Gln | Ser | Leu | Thr | Arg | Thr | Val | Cys | 220 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Gly | Gly | Cys | Ala | Arg | Cys | Lys | Gly | Pro | Leu | Pro | Thr | Asp | Cys | Cys | His | Glu | Gln | Cys | 240 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Ala | Gly | Cys | Thr | Gly | Pro | Lys | His | Ser | Asp | Cys | Leu | Ala | Cys | Leu | His | Phe | Asn | His | 260 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ser | Gly | Ile | Cys | Glu | Leu | His | Cys | Pro | Ala | Leu | Val | Thr | Tyr | Asn | Thr | Asp | Thr | Phe | Glu | 280 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ser | Met | Pro | Asn | Pro | Glu | Gly | Arg | Tyr | Thr | Phe | Gly | Ala | Ser | Cys | Val | Thr | Ala | Cys | Pro | 300 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 310 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 320 |
| Tyr | Asn | Tyr | Leu | Ser | Thr | Asp | Val | Gly | Ser | Cys | Thr | Leu | Val | Cys | Pro | Leu | His | Asn | Gln | 320 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Glu | Val | Thr | Ala | Glu | Asp | Gly | Thr | Gln | Arg | Cys | Glu | Lys | Cys | Ser | Lys | Pro | Cys | Ala | Arg | 340 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Val | Cys | Tyr | Gly | Leu | Gly | Met | Glu | His | Leu | Arg | Glu | Val | Arg | Ala | Val | Thr | Ser | Ala | Asn | 360 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ile | Gln | Glu | Phe | Ala | Gly | Cys | Lys | Lys | Ile | Phe | Gly | Ser | Leu | Ala | Phe | Leu | Pro | Glu | Ser | 380 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Phe | Asp | Gly | Asp | Pro | Ala | Ser | Asn | Thr | Ala | Pro | Leu | Gln | Pro | Glu | Gln | Leu | Gln | Val | Phe | 400 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 410 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 420 |
| Glu | Thr | Leu | Glu | Glu | Ile | Thr | Gly | Tyr | Leu | Tyr | Ile | Ser | Ala | Trp | Pro | Asp | Ser | Leu | Pro | 420 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Asp | Leu | Ser | Val | Phe | Gln | Asn | Leu | Gln | Val | Ile | Arg | Gly | Arg | Ile | Leu | His | Asn | Gly | Ala | 440 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Tyr | Ser | Leu | Thr | Leu | Gln | Gly | Leu | Gly | Ile | Ser | Trp | Leu | Gly | Leu | Arg | Ser | Leu | Arg | Glu | 460 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Gly | Ser | Gly | Leu | Ala | Leu | Ile | His | His | Asn | Thr | His | Leu | Cys | Phe | Val | His | Thr | Val | 480 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Pro | Trp | Asp | Gln | Leu | Phe | Arg | Asn | Pro | His | Gln | Ala | Leu | Leu | His | Thr | Ala | Asn | Arg | Pro | 500 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 510 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 520 |
| Glu | Asp | Glu | Cys | Val | Gly | Glu | Gly | Leu | Ala | Cys | His | Gln | Leu | Cys | Ala | Arg | Gly | His | Cys | 520 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Trp | Gly | Pro | Gly | Pro | Thr | Gln | Cys | Val | Asn | Cys | Ser | Gln | Phe | Leu | Arg | Gly | Gln | Glu | Cys | 540 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Val | Glu | Glu | Cys | Arg | Val | Leu | Gln | Gly | Leu | Pro | Arg | Glu | Tyr | Val | Asn | Ala | Arg | His | Cys | 560 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Pro | Cys | His | Pro | Glu | Cys | Gln | Pro | Gln | Asn | Gly | Ser | Val | Thr | Cys | Phe | Gly | Pro | Glu | 580 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Asp | Gln | Cys | Val | Ala | Cys | Ala | His | Tyr | Lys | Asp | Pro | Pro | Phe | Cys | Val | Ala | Arg | Cys | 600 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |

Fig. 7 (SEQ ID NO: 1)

|      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|
| 610  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 620  |      |
| Pro  | Ser | Gly | Val | Lys | Pro | Asp | Leu | Ser | Tyr | Met | Pro | Ile | Trp | Lys | Phe | Pro | Asp | Glu | Glu  | 620  |
| Gly  | Ala | Cys | Gln | Pro | Cys | Pro | Ile | Asn | Cys | Thr | His | Ser | Cys | Val | Asp | Leu | Asp | Asp | Lys  | 640  |
| Gly  | Cys | Pro | Ala | Glu | Gln | Arg | Ala | Ser | Pro | Leu | Thr | Ser | Ile | Ile | Ser | Ala | Val | Val | Gly  | 660  |
| Ile  | Leu | Leu | Val | Val | Val | Leu | Gly | Val | Val | Phe | Gly | Ile | Leu | Ile | Lys | Arg | Arg | Gln | Gln  | 680  |
| Lys  | Ile | Arg | Lys | Tyr | Thr | Met | Arg | Arg | Leu | Leu | Gln | Glu | Thr | Glu | Leu | Val | Glu | Pro | Leu  | 700  |
| 710  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 720  |      |
| Thr  | Pro | Ser | Gly | Ala | Met | Pro | Asn | Gln | Ala | Gln | Met | Arg | Ile | Leu | Lys | Glu | Thr | Glu | Leu  | 720  |
| Arg  | Lys | Val | Lys | Val | Leu | Gly | Ser | Gly | Ala | Phe | Gly | Thr | Val | Tyr | Lys | Gly | Ile | Trp | Ile  | 740  |
| Pro  | Asp | Gly | Glu | Asn | Val | Lys | Ile | Pro | Val | Ala | Ile | Lys | Val | Leu | Arg | Glu | Asn | Thr | Ser  | 760  |
| Pro  | Lys | Ala | Asn | Lys | Glu | Ile | Leu | Asp | Glu | Ala | Tyr | Val | Met | Ala | Gly | Val | Gly | Ser | Pro  | 780  |
| Tyr  | Val | Ser | Arg | Leu | Leu | Gly | Ile | Cys | Leu | Thr | Ser | Thr | Val | Gln | Leu | Val | Thr | Gln | Leu  | 800  |
| 810  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 820  |      |
| Met  | Pro | Tyr | Gly | Cys | Leu | Leu | Asp | His | Val | Arg | Glu | Asn | Arg | Gly | Arg | Leu | Gly | Ser | Gln  | 820  |
| Asp  | Leu | Leu | Asn | Trp | Cys | Met | Gln | Ile | Ala | Lys | Gly | Met | Ser | Tyr | Leu | Glu | Asp | Val | Arg  | 840  |
| Leu  | Val | His | Arg | Asp | Leu | Ala | Ala | Arg | Asn | Val | Leu | Val | Lys | Ser | Pro | Asn | His | Val | Lys  | 860  |
| Ile  | Thr | Asp | Phe | Gly | Leu | Ala | Arg | Leu | Leu | Asp | Ile | Asp | Glu | Thr | Glu | Tyr | His | Ala | Asp  | 880  |
| Gly  | Gly | Lys | Val | Pro | Ile | Lys | Trp | Met | Ala | Leu | Glu | Ser | Ile | Leu | Arg | Arg | Arg | Phe | Thr  | 900  |
| 910  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 920  |      |
| His  | Gln | Ser | Asp | Val | Trp | Ser | Tyr | Gly | Val | Thr | Val | Trp | Glu | Leu | Met | Thr | Phe | Gly | Ala  | 920  |
| Lys  | Pro | Tyr | Asp | Gly | Ile | Pro | Ala | Arg | Glu | Ile | Pro | Asp | Leu | Leu | Glu | Lys | Gly | Glu | Arg  | 940  |
| Leu  | Pro | Gln | Pro | Pro | Ile | Cys | Thr | Ile | Asp | Val | Tyr | Met | Ile | Met | Val | Lys | Cys | Trp | Met  | 960  |
| Ile  | Asp | Ser | Glu | Cys | Arg | Pro | Arg | Phe | Arg | Glu | Leu | Val | Ser | Glu | Phe | Ser | Arg | Met | Ala  | 980  |
| Arg  | Asp | Pro | Gln | Arg | Phe | Val | Val | Ile | Gln | Asn | Glu | Asp | Leu | Gly | Pro | Ala | Ser | Pro | Leu  | 1000 |
| 1010 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 1020 |      |
| Asp  | Ser | Thr | Phe | Tyr | Arg | Ser | Leu | Leu | Glu | Asp | Asp | Asp | Met | Gly | Asp | Leu | Val | Asp | Ala  | 1020 |
| Glu  | Glu | Tyr | Leu | Val | Pro | Gln | Gln | Gly | Phe | Phe | Cys | Pro | Asp | Pro | Ala | Pro | Gly | Ala | Gly  | 1040 |
| Gly  | Met | Val | His | His | Arg | His | Arg | Ser | Ser | Ser | Thr | Arg | Ser | Gly | Gly | Gly | Asp | Leu | Thr  | 1060 |
| Leu  | Gly | Leu | Glu | Pro | Ser | Glu | Glu | Glu | Ala | Pro | Arg | Ser | Pro | Leu | Ala | Pro | Ser | Glu | Gly  | 1080 |
| Ala  | Gly | Ser | Asp | Val | Phe | Asp | Gly | Asp | Leu | Gly | Met | Gly | Ala | Ala | Lys | Gly | Leu | Gln | Ser  | 1100 |
| 1110 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 1120 |      |
| Leu  | Pro | Thr | His | Asp | Pro | Ser | Pro | Leu | Gln | Arg | Tyr | Ser | Glu | Asp | Pro | Thr | Val | Pro | Leu  | 1120 |
| Pro  | Ser | Glu | Thr | Asp | Gly | Tyr | Val | Ala | Pro | Leu | Thr | Cys | Ser | Pro | Gln | Pro | Glu | Tyr | Val  | 1140 |
| Asn  | Gln | Pro | Asp | Val | Arg | Pro | Gln | Pro | Pro | Ser | Pro | Arg | Glu | Gly | Pro | Leu | Pro | Ala | Ala  | 1160 |
| Arg  | Pro | Ala | Gly | Ala | Thr | Leu | Glu | Arg | Pro | Lys | Thr | Leu | Ser | Pro | Gly | Lys | Asn | Gly | Val  | 1180 |
| Val  | Lys | Asp | Val | Phe | Ala | Phe | Gly | Gly | Ala | Val | Glu | Asn | Pro | Glu | Tyr | Leu | Thr | Pro | Gln  | 1200 |
| 1210 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 1220 |      |
| Gly  | Gly | Ala | Ala | Pro | Gln | Pro | His | Pro | Pro | Pro | Ala | Phe | Ser | Pro | Ala | Phe | Asp | Asn | Leu  | 1220 |
| Tyr  | Tyr | Trp | Asp | Gln | Asp | Pro | Pro | Glu | Arg | Gly | Ala | Pro | Pro | Ser | Thr | Phe | Lys | Gly | Thr  | 1240 |
| Pro  | Thr | Ala | Glu | Asn | Pro | Glu | Tyr | Leu | Gly | Leu | Asp | Val | Pro | Val | .   | .   | .   | .   | .    | 1257 |

Fig. 8 (SEQ ID NO: 2)

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|--|--|--|--|--|-----|--|--|--|--|--|--|--|--|--|
|     |     |     |     |     |     |     |     |     |     | 10  |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  | 20  |  |  |  |  |  |  |  |  |  |
| Met | Glu | Leu | Ala | Ala | Trp | Cys | Arg | Trp | Gly | Phe | Leu | Leu | Ala | Leu | Leu | Pro | Pro | Gly | Ile | 20  |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Ala | Gly | Thr | Gln | Val | Cys | Thr | Gly | Thr | Asp | Met | Lys | Leu | Arg | Leu | Pro | Ala | Ser | Pro | Glu | 40  |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Thr | His | Leu | Asp | Met | Leu | Arg | His | Leu | Tyr | Gln | Gly | Cys | Gln | Val | Val | Gln | Gly | Asn | Leu | 60  |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Glu | Leu | Thr | Tyr | Val | Pro | Ala | Asn | Ala | Ser | Leu | Ser | Phe | Leu | Gln | Asp | Ile | Gln | Glu | Val | 80  |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Gln | Gly | Tyr | Met | Leu | Ile | Ala | His | Asn | Gln | Val | Lys | Arg | Val | Pro | Leu | Gln | Arg | Leu | Arg | 100 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     |     |     |     |     |     |     |     |     | 110 |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  | 120 |  |  |  |  |  |  |  |  |  |
| Ile | Val | Arg | Gly | Thr | Gln | Leu | Phe | Glu | Asp | Lys | Tyr | Ala | Leu | Ala | Val | Leu | Asp | Asn | Arg | 120 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Asp | Pro | Gln | Asp | Asn | Val | Ala | Ala | Ser | Thr | Pro | Gly | Arg | Thr | Pro | Glu | Gly | Leu | Arg | Glu | 140 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Leu | Gln | Leu | Arg | Ser | Leu | Thr | Glu | Ile | Leu | Lys | Gly | Gly | Val | Leu | Ile | Arg | Gly | Asn | Pro | 160 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Gln | Leu | Cys | Tyr | Gln | Asp | Met | Val | Leu | Trp | Lys | Asp | Val | Phe | Arg | Lys | Asn | Asn | Gln | Leu | 180 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Ala | Pro | Val | Asp | Ile | Asp | Thr | Asn | Arg | Ser | Arg | Ala | Cys | Pro | Pro | Cys | Ala | Pro | Ala | Cys | 200 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     |     |     |     |     |     |     |     |     | 210 |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  | 220 |  |  |  |  |  |  |  |  |  |
| Lys | Asp | Asn | His | Cys | Trp | Gly | Glu | Ser | Pro | Glu | Asp | Cys | Gln | Ile | Leu | Thr | Gly | Thr | Ile | 220 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Cys | Thr | Ser | Gly | Cys | Ala | Arg | Cys | Lys | Gly | Arg | Leu | Pro | Thr | Asp | Cys | Cys | His | Glu | Gln | 240 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Cys | Ala | Ala | Gly | Cys | Thr | Gly | Pro | Lys | His | Ser | Asp | Cys | Leu | Ala | Cys | Leu | His | Phe | Asn | 260 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| His | Ser | Gly | Ile | Cys | Glu | Leu | His | Cys | Pro | Ala | Leu | Val | Thr | Tyr | Asn | Thr | Asp | Thr | Phe | 280 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Glu | Ser | Met | His | Asn | Pro | Glu | Gly | Arg | Tyr | Thr | Phe | Gly | Ala | Ser | Cys | Val | Thr | Thr | Cys | 300 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     |     |     |     |     |     |     |     |     | 310 |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  | 320 |  |  |  |  |  |  |  |  |  |
| Pro | Tyr | Asn | Tyr | Leu | Ser | Thr | Glu | Val | Gly | Ser | Cys | Thr | Leu | Val | Cys | Pro | Pro | Asn | Asn | 320 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Gln | Glu | Val | Thr | Ala | Glu | Asp | Gly | Thr | Gln | Arg | Cys | Glu | Lys | Cys | Ser | Lys | Pro | Cys | Ala | 340 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Arg | Val | Cys | Tyr | Gly | Leu | Gly | Met | Glu | His | Leu | Arg | Gly | Ala | Arg | Ala | Ile | Thr | Ser | Asp | 360 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Asn | Val | Gln | Glu | Phe | Asp | Gly | Cys | Lys | Lys | Ile | Phe | Gly | Ser | Leu | Ala | Phe | Leu | Pro | Glu | 380 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Ser | Phe | Asp | Gly | Asp | Pro | Ser | Ser | Gly | Ile | Ala | Pro | Leu | Arg | Pro | Glu | Gln | Leu | Gln | Val | 400 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     |     |     |     |     |     |     |     |     | 410 |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  | 420 |  |  |  |  |  |  |  |  |  |
| Phe | Glu | Thr | Leu | Glu | Glu | Ile | Thr | Gly | Tyr | Leu | Tyr | Ile | Ser | Ala | Trp | Pro | Asp | Ser | Leu | 420 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Arg | Asp | Leu | Ser | Val | Phe | Gln | Asn | Leu | Arg | Ile | Ile | Arg | Gly | Arg | Ile | Leu | His | Asp | Gly | 440 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Ala | Tyr | Ser | Leu | Thr | Leu | Gln | Gly | Leu | Gly | Ile | His | Ser | Leu | Gly | Leu | Arg | Ser | Leu | Arg | 460 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Glu | Leu | Gly | Ser | Gly | Leu | Ala | Leu | Ile | His | Arg | Asn | Ala | His | Leu | Cys | Phe | Val | His | Thr | 480 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Val | Pro | Trp | Asp | Gln | Leu | Phe | Arg | Asn | Pro | His | Gln | Ala | Leu | Leu | His | Ser | Gly | Asn | Arg | 500 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     |     |     |     |     |     |     |     |     | 510 |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  | 520 |  |  |  |  |  |  |  |  |  |
| Pro | Glu | Glu | Asp | Cys | Gly | Leu | Glu | Gly | Leu | Val | Cys | Asn | Ser | Leu | Cys | Ala | His | Gly | His | 520 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Cys | Trp | Gly | Pro | Gly | Pro | Thr | Gln | Cys | Val | Asn | Cys | Ser | His | Phe | Leu | Arg | Gly | Gln | Glu | 540 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Cys | Val | Glu | Glu | Cys | Arg | Val | Trp | Lys | Gly | Leu | Pro | Arg | Glu | Tyr | Val | Ser | Asp | Lys | Arg | 560 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Cys | Leu | Pro | Cys | His | Pro | Glu | Cys | Gln | Pro | Gln | Asn | Ser | Ser | Glu | Thr | Cys | Phe | Gly | Ser | 580 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Glu | Ala | Asp | Gln | Cys | Ala | Ala | Cys | Ala | His | Tyr | Lys | Asp | Ser | Ser | Ser | Cys | Val | Ala | Arg | 600 |  |  |  |  |  |  |  |  |  |     |  |  |  |  |  |  |  |  |  |



Fig. 8 (SEQ ID NO: 2)

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |  |  |      |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|--|--|------|--|--|
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 610  |      |  |  | 620  |  |  |
| Cys | Pro | Ser | Gly | Val | Lys | Pro | Asp | Leu | Ser | Tyr | Met | Pro | Ile | Trp | Lys | Tyr | Pro | Asp | Glu  | 620  |  |  |      |  |  |
| Glu | Gly | Ile | Cys | Gln | Pro | Cys | Pro | Ile | Asn | Cys | Thr | His | Ser | Cys | Val | Asp | Leu | Asp | Glu  | 640  |  |  |      |  |  |
| Arg | Gly | Cys | Pro | Ala | Glu | Gln | Arg | Ala | Ser | Pro | Val | Thr | Phe | Ile | Ile | Ala | Thr | Val | Val  | 660  |  |  |      |  |  |
| Gly | Val | Leu | Leu | Phe | Leu | Ile | Leu | Val | Val | Val | Val | Gly | Ile | Leu | Ile | Lys | Arg | Arg | Arg  | 680  |  |  |      |  |  |
| Gln | Lys | Ile | Arg | Lys | Tyr | Thr | Met | Arg | Arg | Leu | Leu | Gln | Glu | Thr | Glu | Leu | Val | Glu | Pro  | 700  |  |  |      |  |  |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 710  |      |  |  | 720  |  |  |
| Leu | Thr | Pro | Ser | Gly | Ala | Met | Pro | Asn | Gln | Ala | Gln | Met | Arg | Ile | Leu | Lys | Glu | Thr | Glu  | 720  |  |  |      |  |  |
| Leu | Arg | Lys | Val | Lys | Val | Leu | Gly | Ser | Gly | Ala | Phe | Gly | Thr | Val | Tyr | Lys | Gly | Ile | Trp  | 740  |  |  |      |  |  |
| Ile | Pro | Asp | Gly | Glu | Asn | Val | Lys | Ile | Pro | Val | Ala | Ile | Lys | Val | Leu | Arg | Glu | Asn | Thr  | 760  |  |  |      |  |  |
| Ser | Pro | Lys | Ala | Asn | Lys | Glu | Ile | Leu | Asp | Glu | Ala | Tyr | Val | Met | Ala | Gly | Val | Gly | Ser  | 780  |  |  |      |  |  |
| Pro | Tyr | Val | Ser | Arg | Leu | Leu | Gly | Ile | Cys | Leu | Thr | Ser | Thr | Val | Gln | Leu | Val | Thr | Gln  | 800  |  |  |      |  |  |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 810  |      |  |  | 820  |  |  |
| Leu | Met | Pro | Tyr | Gly | Cys | Leu | Leu | Asp | His | Val | Arg | Glu | His | Arg | Gly | Arg | Leu | Gly | Ser  | 820  |  |  |      |  |  |
| Gln | Asp | Leu | Leu | Asn | Trp | Cys | Val | Gln | Ile | Ala | Lys | Gly | Met | Ser | Tyr | Leu | Glu | Asp | Val  | 840  |  |  |      |  |  |
| Arg | Leu | Val | His | Arg | Asp | Leu | Ala | Ala | Arg | Asn | Val | Leu | Val | Lys | Ser | Pro | Asn | His | Val  | 860  |  |  |      |  |  |
| Lys | Ile | Thr | Asp | Phe | Gly | Leu | Ala | Arg | Leu | Leu | Asp | Ile | Asp | Glu | Thr | Glu | Tyr | His | Ala  | 880  |  |  |      |  |  |
| Asp | Gly | Gly | Lys | Val | Pro | Ile | Lys | Trp | Met | Ala | Leu | Glu | Ser | Ile | Leu | Arg | Arg | Arg | Phe  | 900  |  |  |      |  |  |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 910  |      |  |  | 920  |  |  |
| Thr | His | Gln | Ser | Asp | Val | Trp | Ser | Tyr | Gly | Val | Thr | Val | Trp | Glu | Leu | Met | Thr | Phe | Gly  | 920  |  |  |      |  |  |
| Ala | Lys | Pro | Tyr | Asp | Gly | Ile | Pro | Ala | Arg | Glu | Ile | Pro | Asp | Leu | Leu | Glu | Lys | Gly | Glu  | 940  |  |  |      |  |  |
| Arg | Leu | Pro | Gln | Pro | Pro | Ile | Cys | Thr | Ile | Asp | Val | Tyr | Met | Ile | Met | Val | Lys | Cys | Trp  | 960  |  |  |      |  |  |
| Met | Ile | Asp | Ser | Glu | Cys | Arg | Pro | Arg | Phe | Arg | Glu | Leu | Val | Ser | Glu | Phe | Ser | Arg | Met  | 980  |  |  |      |  |  |
| Ala | Arg | Asp | Pro | Gln | Arg | Phe | Val | Val | Ile | Gln | Asn | Glu | Asp | Leu | Gly | Pro | Ser | Ser | Pro  | 1000 |  |  |      |  |  |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 1010 |      |  |  | 1020 |  |  |
| Met | Asp | Ser | Thr | Phe | Tyr | Arg | Ser | Leu | Leu | Glu | Asp | Asp | Asp | Met | Gly | Asp | Leu | Val | Asp  | 1020 |  |  |      |  |  |
| Ala | Glu | Glu | Tyr | Leu | Val | Pro | Gln | Gln | Gly | Phe | Phe | Ser | Pro | Asp | Pro | Thr | Pro | Gly | Thr  | 1040 |  |  |      |  |  |
| Gly | Ser | Thr | Ala | His | Arg | Arg | His | Arg | Ser | Ser | Ser | Thr | Arg | Ser | Gly | Gly | Gly | Glu | Leu  | 1060 |  |  |      |  |  |
| Thr | Leu | Gly | Leu | Glu | Pro | Ser | Glu | Glu | Gly | Pro | Pro | Arg | Ser | Pro | Leu | Ala | Pro | Ser | Glu  | 1080 |  |  |      |  |  |
| Gly | Ala | Gly | Ser | Asp | Val | Phe | Asp | Gly | Asp | Leu | Ala | Met | Gly | Val | Thr | Lys | Gly | Leu | Gln  | 1100 |  |  |      |  |  |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 1110 |      |  |  | 1120 |  |  |
| Ser | Leu | Ser | Pro | His | Asp | Leu | Ser | Pro | Leu | Gln | Arg | Tyr | Ser | Glu | Asp | Pro | Thr | Leu | Pro  | 1120 |  |  |      |  |  |
| Leu | Pro | Pro | Glu | Thr | Asp | Gly | Tyr | Val | Ala | Pro | Leu | Ala | Cys | Ser | Pro | Gln | Pro | Glu | Tyr  | 1140 |  |  |      |  |  |
| Val | Asn | Gln | Ser | Glu | Val | Gln | Pro | Gln | Pro | Pro | Leu | Thr | Pro | Glu | Gly | Pro | Leu | Pro | Pro  | 1160 |  |  |      |  |  |
| Val | Arg | Pro | Ala | Gly | Ala | Thr | Leu | Glu | Arg | Pro | Lys | Thr | Leu | Ser | Pro | Gly | Lys | Asn | Gly  | 1180 |  |  |      |  |  |
| Val | Val | Lys | Asp | Val | Phe | Ala | Phe | Gly | Gly | Ala | Val | Glu | Asn | Pro | Glu | Tyr | Leu | Val | Pro  | 1200 |  |  |      |  |  |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 1210 |      |  |  | 1220 |  |  |
| Arg | Glu | Gly | Thr | Ala | Ser | Pro | Pro | His | Pro | Ser | Pro | Ala | Phe | Ser | Pro | Ala | Phe | Asp | Asn  | 1220 |  |  |      |  |  |
| Leu | Tyr | Tyr | Trp | Asp | Gln | Asn | Ser | Ser | Glu | Gln | Gly | Pro | Pro | Pro | Ser | Asn | Phe | Glu | Gly  | 1240 |  |  |      |  |  |
| Thr | Pro | Thr | Ala | Glu | Asn | Pro | Glu | Tyr | Leu | Gly | Leu | Asp | Val | Pro | Val | .   | .   | .   | .    | 1258 |  |  |      |  |  |

Fig. 9 (SEQ ID NO: 3)

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|-----|
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 10  |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 20  |
| Met | Glu | Leu | Ala | Ala | Leu | Cys | Arg | Trp | Gly | Leu | Leu | Leu | Ala | Leu | Leu | Pro | Pro | Gly | Ala | 20  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Ser | Thr | Gln | Val | Cys | Thr | Gly | Thr | Asp | Met | Lys | Leu | Arg | Leu | Pro | Ala | Ser | Pro | Glu | 40  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Thr | His | Leu | Asp | Met | Leu | Arg | His | Leu | Tyr | Gln | Gly | Cys | Gln | Val | Val | Gln | Gly | Asn | Leu | 60  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Glu | Leu | Thr | Tyr | Leu | Pro | Thr | Asn | Ala | Ser | Leu | Ser | Phe | Leu | Gln | Asp | Ile | Gln | Glu | Val | 80  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Gln | Gly | Tyr | Val | Leu | Ile | Ala | His | Asn | Gln | Val | Arg | Gln | Val | Pro | Leu | Gln | Arg | Leu | Arg | 100 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 110 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 120 |
| Ile | Val | Arg | Gly | Thr | Gln | Leu | Phe | Glu | Asp | Asn | Tyr | Ala | Leu | Ala | Val | Leu | Asp | Asn | Gly | 120 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Asp | Pro | Leu | Asn | Asn | Thr | Thr | Pro | Val | Thr | Gly | Ala | Ser | Pro | Gly | Gly | Leu | Arg | Glu | Leu | 140 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Gln | Leu | Arg | Ser | Leu | Thr | Glu | Ile | Leu | Lys | Gly | Gly | Val | Leu | Ile | Gln | Arg | Asn | Pro | Gln | 160 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Cys | Tyr | Gln | Asp | Thr | Ile | Leu | Trp | Lys | Asp | Ile | Phe | His | Lys | Asn | Asn | Gln | Leu | Ala | 180 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Thr | Leu | Ile | Asp | Thr | Asn | Arg | Ser | Arg | Ala | Cys | His | Pro | Cys | Ser | Pro | Met | Cys | Lys | 200 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 210 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 220 |
| Gly | Ser | Arg | Cys | Trp | Gly | Glu | Ser | Ser | Glu | Asp | Cys | Gln | Ser | Leu | Thr | Arg | Thr | Val | Cys | 220 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Gly | Gly | Cys | Ala | Arg | Cys | Lys | Gly | Pro | Leu | Pro | Thr | Asp | Cys | Cys | His | Glu | Gln | Cys | 240 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Ala | Gly | Cys | Thr | Gly | Pro | Lys | His | Ser | Asp | Cys | Leu | Ala | Cys | Leu | His | Phe | Asn | His | 260 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ser | Gly | Ile | Cys | Glu | Leu | His | Cys | Pro | Ala | Leu | Val | Thr | Tyr | Asn | Thr | Asp | Thr | Phe | Glu | 280 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ser | Met | Pro | Asn | Pro | Glu | Gly | Arg | Tyr | Thr | Phe | Gly | Ala | Ser | Cys | Val | Thr | Ala | Cys | Pro | 300 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 310 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 320 |
| Tyr | Asn | Tyr | Leu | Ser | Thr | Asp | Val | Gly | Ser | Cys | Thr | Leu | Val | Cys | Pro | Leu | His | Asn | Gln | 320 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Glu | Val | Thr | Ala | Glu | Asp | Gly | Thr | Gln | Arg | Cys | Glu | Lys | Cys | Ser | Lys | Pro | Cys | Ala | Arg | 340 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Val | Cys | Tyr | Gly | Leu | Gly | Met | Glu | His | Leu | Arg | Glu | Val | Arg | Ala | Val | Thr | Ser | Ala | Asn | 360 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ile | Gln | Glu | Phe | Ala | Gly | Cys | Lys | Lys | Ile | Phe | Gly | Ser | Leu | Ala | Phe | Leu | Pro | Glu | Ser | 380 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Phe | Asp | Gly | Asp | Pro | Ala | Ser | Asn | Thr | Ala | Pro | Leu | Gln | Pro | Glu | Gln | Leu | Gln | Val | Phe | 400 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 410 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 420 |
| Glu | Thr | Leu | Glu | Glu | Ile | Thr | Gly | Tyr | Leu | Tyr | Ile | Ser | Ala | Trp | Pro | Asp | Ser | Leu | Pro | 420 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Asp | Leu | Ser | Val | Phe | Gln | Asn | Leu | Gln | Val | Ile | Arg | Gly | Arg | Ile | Leu | His | Asn | Gly | Ala | 440 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Tyr | Ser | Leu | Thr | Leu | Gln | Gly | Leu | Gly | Ile | Ser | Trp | Leu | Gly | Leu | Arg | Ser | Leu | Arg | Glu | 460 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Gly | Ser | Gly | Leu | Ala | Leu | Ile | His | His | Asn | Thr | His | Leu | Cys | Phe | Val | His | Thr | Val | 480 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Pro | Trp | Asp | Gln | Leu | Phe | Arg | Asn | Pro | His | Gln | Ala | Leu | Leu | His | Thr | Ala | Asn | Arg | Pro | 500 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 510 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 520 |
| Glu | Asp | Glu | Cys | Val | Gly | Glu | Gly | Leu | Ala | Cys | His | Gln | Leu | Cys | Ala | Arg | Gly | His | Cys | 520 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Trp | Gly | Pro | Gly | Pro | Thr | Gln | Cys | Val | Asn | Cys | Ser | Gln | Phe | Leu | Arg | Gly | Gln | Glu | Cys | 540 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Val | Glu | Glu | Cys | Arg | Val | Leu | Gln | Gly | Leu | Pro | Arg | Glu | Tyr | Val | Asn | Ala | Arg | His | Cys | 560 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Pro | Cys | His | Pro | Glu | Cys | Gln | Pro | Gln | Asn | Gly | Ser | Val | Thr | Cys | Phe | Gly | Pro | Glu | 580 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Asp | Gln | Cys | Val | Ala | Cys | Ala | His | Tyr | Lys | Asp | Pro | Pro | Phe | Cys | Val | Ala | Arg | Cys | 600 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 610 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 620 |
| Pro | Ser | Gly | Val | Lys | Pro | Asp | Leu | Ser | Tyr | Met | Pro | Ile | Trp | Lys | Phe | Pro | Asp | Glu | Glu | 620 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Gly | Ala | Cys | Gln | Pro | Cys | Pro | Ile | Asn | Cys | Thr | His | Ser | Cys | Val | Asp | Leu | Asp | Asp | Lys | 640 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Gly | Cys | Pro | Ala | Glu | Gln | Arg | Ala | Ser | Pro | Leu | Thr | Ser | 653 |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |

Fig. 10 (SEQ ID NO: 4)

[illegible]

**Fig. 11** (SEQ ID NO: 5)

[illegible]

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|-----|
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 10  |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 20  |
| Met | Glu | Leu | Ala | Ala | Leu | Cys | Arg | Trp | Gly | Leu | Leu | Leu | Ala | Leu | Leu | Pro | Pro | Gly | Ala | 20  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Ser | Thr | Gln | Val | Cys | Thr | Gly | Thr | Asp | Met | Lys | Leu | Arg | Leu | Pro | Ala | Ser | Pro | Glu | 40  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Thr | His | Leu | Asp | Met | Leu | Arg | His | Leu | Tyr | Gln | Gly | Cys | Gln | Val | Val | Gln | Gly | Asn | Leu | 60  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Glu | Leu | Thr | Tyr | Leu | Pro | Thr | Asn | Ala | Ser | Leu | Ser | Phe | Leu | Gln | Asp | Ile | Gln | Glu | Val | 80  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Gln | Gly | Tyr | Val | Leu | Ile | Ala | His | Asn | Gln | Val | Arg | Gln | Val | Pro | Leu | Gln | Arg | Leu | Arg | 100 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 110 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 120 |
| Ile | Val | Arg | Gly | Thr | Gln | Leu | Phe | Glu | Asp | Asn | Tyr | Ala | Leu | Ala | Val | Leu | Asp | Asn | Gly | 120 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Asp | Pro | Leu | Asn | Asn | Thr | Thr | Pro | Val | Thr | Gly | Ala | Ser | Pro | Gly | Gly | Leu | Arg | Glu | Leu | 140 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Gln | Leu | Arg | Ser | Leu | Thr | Glu | Ile | Leu | Lys | Gly | Gly | Val | Leu | Ile | Gln | Arg | Asn | Pro | Gln | 160 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Cys | Tyr | Gln | Asp | Thr | Ile | Leu | Trp | Lys | Asp | Ile | Phe | His | Lys | Asn | Asn | Gln | Leu | Ala | 180 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Thr | Leu | Ile | Asp | Thr | Asn | Arg | Ser | Arg | Ala | Cys | His | Pro | Cys | Ser | Pro | Met | Cys | Lys | 200 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 210 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 220 |
| Gly | Ser | Arg | Cys | Trp | Gly | Glu | Ser | Ser | Glu | Asp | Cys | Gln | Ser | Leu | Thr | Arg | Thr | Val | Cys | 220 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Gly | Gly | Cys | Ala | Arg | Cys | Lys | Gly | Pro | Leu | Pro | Thr | Asp | Cys | Cys | His | Glu | Gln | Cys | 240 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Ala | Gly | Cys | Thr | Gly | Pro | Lys | His | Ser | Asp | Cys | Leu | Ala | Cys | Leu | His | Phe | Asn | His | 260 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ser | Gly | Ile | Cys | Glu | Leu | His | Cys | Pro | Ala | Leu | Val | Thr | Tyr | Asn | Thr | Asp | Thr | Phe | Glu | 280 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ser | Met | Pro | Asn | Pro | Glu | Gly | Arg | Tyr | Thr | Phe | Gly | Ala | Ser | Cys | Val | Thr | Ala | Cys | Pro | 300 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 310 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 320 |
| Tyr | Asn | Tyr | Leu | Ser | Thr | Asp | Val | Gly | Ser | Cys | Thr | Leu | Val | Cys | Pro | Leu | His | Asn | Gln | 320 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Glu | Val | Thr | Ala | Glu | Asp | Gly | Thr | Gln | Arg | Cys | Glu | Lys | Cys | Ser | Lys | Pro | Cys | Ala | Arg | 340 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Val | Cys | Tyr | Gly | Leu | Gly | Met | Glu | His | Leu | Arg | Glu | Val | Arg | Ala | Val | Thr | Ser | Ala | Asn | 360 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ile | Gln | Glu | Phe | Ala | Gly | Cys | Lys | Lys | Ile | Phe | Gly | Ser | Leu | Ala | Phe | Leu | Pro | Glu | Ser | 380 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Phe | Asp | Gly | Asp | Pro | Ala | Ser | Asn | Thr | Ala | Pro | Leu | Gln | Pro | Glu | Gln | Leu | Gln | Val | Phe | 400 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 410 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 420 |
| Glu | Thr | Leu | Glu | Glu | Ile | Thr | Gly | Tyr | Leu | Tyr | Ile | Ser | Ala | Trp | Pro | Asp | Ser | Leu | Pro | 420 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Asp | Leu | Ser | Val | Phe | Gln | Asn | Leu | Gln | Val | Ile | Arg | Gly | Arg | Ile | Leu | His | Asn | Gly | Ala | 440 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Tyr | Ser | Leu | Thr | Leu | Gln | Gly | Leu | Gly | Ile | Ser | Trp | Leu | Gly | Leu | Arg | Ser | Leu | Arg | Glu | 460 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Gly | Ser | Gly | Leu | Ala | Leu | Ile | His | His | Asn | Thr | His | Leu | Cys | Phe | Val | His | Thr | Val | 480 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Pro | Trp | Asp | Gln | Leu | Phe | Arg | Asn | Pro | His | Gln | Ala | Leu | Leu | His | Thr | Ala | Asn | Arg | Pro | 500 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 510 |     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 520 |
| Glu | Asp | Glu | Cys | Val | Gly | Glu | Gly | Leu | Ala | Cys | His | Gln | Leu | Cys | Ala | Arg | Gly | His | Cys | 520 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Trp | Gly | Pro | Gly | Pro | Thr | Gln | Cys | Val | Asn | Cys | Ser | Gln | Phe | Leu | Arg | Gly | Gln | Glu | Cys | 540 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Val | Glu | Glu | Cys | Arg | Val | Leu | Gln | Gly | Leu | Pro | Arg | Glu | Tyr | Val | Asn | Ala | Arg | His | Cys | 560 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Leu | Pro | Cys | His | Pro | Glu | Cys | Gln | Pro | Gln | Asn | Gly | Ser | Val | Thr | Cys | Phe | Gly | Pro | Glu | 580 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |
| Ala | Asp | Gln | Cys | Val | Ala | Cys | Ala | His | Tyr | Lys | Asp | Pro | Pro | Phe | Cys | Val | Ala | Arg | Cys | 600 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |     |

Fig. 12 (SEQ ID NO: 6)

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 610 |     |     |     |     |     |     |     |     |     | 620 |     |     |     |     |     |     |     |     |     |     |
| Pro | Ser | Gly | Val | Lys | Pro | Asp | Leu | Ser | Tyr | Met | Pro | Ile | Trp | Lys | Phe | Pro | Asp | Glu | Glu | 620 |
| Gly | Ala | Cys | Gln | Pro | Cys | Pro | Ile | Asn | Cys | Thr | His | Ser | Cys | Val | Asp | Leu | Asp | Asp | Lys | 640 |
| Gly | Cys | Pro | Ala | Glu | Gln | Arg | Ala | Ser | Pro | Leu | Thr | Ser | Gln | Asn | Glu | Asp | Leu | Gly | Pro | 660 |
| Ala | Ser | Pro | Leu | Asp | Ser | Thr | Phe | Tyr | Arg | Ser | Leu | Leu | Glu | Asp | Asp | Asp | Met | Gly | Asp | 680 |
| Leu | Val | Asp | Ala | Glu | Glu | Tyr | Leu | Val | Pro | Gln | Gln | Gly | Phe | Phe | Cys | Pro | Asp | Pro | Ala | 700 |
| 710 |     |     |     |     |     |     |     |     |     | 720 |     |     |     |     |     |     |     |     |     |     |
| Pro | Gly | Ala | Gly | Gly | Met | Val | His | His | Arg | His | Arg | Ser | Ser | Ser | Thr | Arg | Ser | Gly | Gly | 720 |
| Gly | Asp | Leu | Thr | Leu | Gly | Leu | Glu | Pro | Ser | Glu | Glu | Glu | Ala | Pro | Arg | Ser | Pro | Leu | Ala | 740 |
| Pro | Ser | Glu | Gly | Ala | Gly | Ser | Asp | Val | Phe | Asp | Gly | Asp | Leu | Gly | Met | Gly | Ala | Ala | Lys | 760 |
| Gly | Leu | Gln | Ser | Leu | Pro | Thr | His | Asp | Pro | Ser | Pro | Leu | Gln | Arg | Tyr | Ser | Glu | Asp | Pro | 780 |
| Thr | Val | Pro | Leu | Pro | Ser | Glu | Thr | Asp | Gly | Tyr | Val | Ala | Pro | Leu | Thr | Cys | Ser | Pro | Gln | 800 |
| 810 |     |     |     |     |     |     |     |     |     | 820 |     |     |     |     |     |     |     |     |     |     |
| Pro | Glu | Tyr | Val | Asn | Gln | Pro | Asp | Val | Arg | Pro | Gln | Pro | Pro | Ser | Pro | Arg | Glu | Gly | Pro | 820 |
| Leu | Pro | Ala | Ala | Arg | Pro | Ala | Gly | Ala | Thr | Leu | Glu | Arg | Pro | Lys | Thr | Leu | Ser | Pro | Gly | 840 |
| Lys | Asn | Gly | Val | Val | Lys | Asp | Val | Phe | Ala | Phe | Gly | Gly | Ala | Val | Glu | Asn | Pro | Glu | Tyr | 860 |
| Leu | Thr | Pro | Gln | Gly | Gly | Ala | Ala | Pro | Gln | Pro | His | Pro | Pro | Pro | Ala | Phe | Ser | Pro | Ala | 880 |
| Phe | Asp | Asn | Leu | Tyr | Tyr | Trp | Asp | Gln | Asp | Pro | Pro | Glu | Arg | Gly | Ala | Pro | Pro | Ser | Thr | 900 |
| 910 |     |     |     |     |     |     |     |     |     | 920 |     |     |     |     |     |     |     |     |     |     |
| Phe | Lys | Gly | Thr | Pro | Thr | Ala | Glu | Asn | Pro | Glu | Tyr | Leu | Gly | Leu | Asp | Val | Pro | Val | •   | 920 |

Pro Gly Ala Gly Gly Met Val His His Arg His Arg • • 714

Fig. 14 (SEQ ID NO: 8)

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|-----|
|     |     |     |     |     |     |     |     |     |     | 10  |     |     |     |     |     |     |     |     |     |  | 20  |
| Met | Glu | Leu | Ala | Ala | Trp | Cys | Arg | Trp | Gly | Phe | Leu | Leu | Ala | Leu | Leu | Pro | Pro | Gly | Ile |  | 20  |
| Ala | Gly | Thr | Gln | Val | Cys | Thr | Gly | Thr | Asp | Met | Lys | Leu | Arg | Leu | Pro | Ala | Ser | Pro | Glu |  | 40  |
| Thr | His | Leu | Asp | Met | Leu | Arg | His | Leu | Tyr | Gln | Gly | Cys | Gln | Val | Val | Gln | Gly | Asn | Leu |  | 60  |
| Glu | Leu | Thr | Tyr | Val | Pro | Ala | Asn | Ala | Ser | Leu | Ser | Phe | Leu | Gln | Asp | Ile | Gln | Glu | Val |  | 80  |
| Gln | Gly | Tyr | Met | Leu | Ile | Ala | His | Asn | Gln | Val | Lys | Arg | Val | Pro | Leu | Gln | Arg | Leu | Arg |  | 100 |
|     |     |     |     |     |     |     |     |     |     | 110 |     |     |     |     |     |     |     |     |     |  | 120 |
| Ile | Val | Arg | Gly | Thr | Gln | Leu | Phe | Glu | Asp | Lys | Tyr | Ala | Leu | Ala | Val | Leu | Asp | Asn | Arg |  | 120 |
| Asp | Pro | Gln | Asp | Asn | Val | Ala | Ala | Ser | Thr | Pro | Gly | Arg | Thr | Pro | Glu | Gly | Leu | Arg | Glu |  | 140 |
| Leu | Gln | Leu | Arg | Ser | Leu | Thr | Glu | Ile | Leu | Lys | Gly | Gly | Val | Leu | Ile | Arg | Gly | Asn | Pro |  | 160 |
| Gln | Leu | Cys | Tyr | Gln | Asp | Met | Val | Leu | Trp | Lys | Asp | Val | Phe | Arg | Lys | Asn | Asn | Gln | Leu |  | 180 |
| Ala | Pro | Val | Asp | Ile | Asp | Thr | Asn | Arg | Ser | Arg | Ala | Cys | Pro | Pro | Cys | Ala | Pro | Ala | Cys |  | 200 |
|     |     |     |     |     |     |     |     |     |     | 210 |     |     |     |     |     |     |     |     |     |  | 220 |
| Lys | Asp | Asn | His | Cys | Trp | Gly | Glu | Ser | Pro | Glu | Asp | Cys | Gln | Ile | Leu | Thr | Gly | Thr | Ile |  | 220 |
| Cys | Thr | Ser | Gly | Cys | Ala | Arg | Cys | Lys | Gly | Arg | Leu | Pro | Thr | Asp | Cys | Cys | His | Glu | Gln |  | 240 |
| Cys | Ala | Ala | Gly | Cys | Thr | Gly | Pro | Lys | His | Ser | Asp | Cys | Leu | Ala | Cys | Leu | His | Phe | Asn |  | 260 |
| His | Ser | Gly | Ile | Cys | Glu | Leu | His | Cys | Pro | Ala | Leu | Val | Thr | Tyr | Asn | Thr | Asp | Thr | Phe |  | 280 |
| Glu | Ser | Met | His | Asn | Pro | Glu | Gly | Arg | Tyr | Thr | Phe | Gly | Ala | Ser | Cys | Val | Thr | Thr | Cys |  | 300 |
|     |     |     |     |     |     |     |     |     |     | 310 |     |     |     |     |     |     |     |     |     |  | 320 |
| Pro | Tyr | Asn | Tyr | Leu | Ser | Thr | Glu | Val | Gly | Ser | Cys | Thr | Leu | Val | Cys | Pro | Pro | Asn | Asn |  | 320 |
| Gln | Glu | Val | Thr | Ala | Glu | Asp | Gly | Thr | Gln | Arg | Cys | Glu | Lys | Cys | Ser | Lys | Pro | Cys | Ala |  | 340 |
| Arg | Val | Cys | Tyr | Gly | Leu | Gly | Met | Glu | His | Leu | Arg | Gly | Ala | Arg | Ala | Ile | Thr | Ser | Asp |  | 360 |
| Asn | Val | Gln | Glu | Phe | Asp | Gly | Cys | Lys | Lys | Ile | Phe | Gly | Ser | Leu | Ala | Phe | Leu | Pro | Glu |  | 380 |
| Ser | Phe | Asp | Gly | Asp | Pro | Ser | Ser | Gly | Ile | Ala | Pro | Leu | Arg | Pro | Glu | Gln | Leu | Gln | Val |  | 400 |
|     |     |     |     |     |     |     |     |     |     | 410 |     |     |     |     |     |     |     |     |     |  | 420 |
| Phe | Glu | Thr | Leu | Glu | Glu | Ile | Thr | Gly | Tyr | Leu | Tyr | Ile | Ser | Ala | Trp | Pro | Asp | Ser | Leu |  | 420 |
| Arg | Asp | Leu | Ser | Val | Phe | Gln | Asn | Leu | Arg | Ile | Ile | Arg | Gly | Arg | Ile | Leu | His | Asp | Gly |  | 440 |
| Ala | Tyr | Ser | Leu | Thr | Leu | Gln | Gly | Leu | Gly | Ile | His | Ser | Leu | Gly | Leu | Arg | Ser | Leu | Arg |  | 460 |
| Glu | Leu | Gly | Ser | Gly | Leu | Ala | Leu | Ile | His | Arg | Asn | Ala | His | Leu | Cys | Phe | Val | His | Thr |  | 480 |
| Val | Pro | Trp | Asp | Gln | Leu | Phe | Arg | Asn | Pro | His | Gln | Ala | Leu | Leu | His | Ser | Gly | Asn | Arg |  | 500 |
|     |     |     |     |     |     |     |     |     |     | 510 |     |     |     |     |     |     |     |     |     |  | 520 |
| Pro | Glu | Glu | Asp | Cys | Gly | Leu | Glu | Gly | Leu | Val | Cys | Asn | Ser | Leu | Cys | Ala | His | Gly | His |  | 520 |
| Cys | Trp | Gly | Pro | Gly | Pro | Thr | Gln | Cys | Val | Asn | Cys | Ser | His | Phe | Leu | Arg | Gly | Gln | Glu |  | 540 |
| Cys | Val | Glu | Glu | Cys | Arg | Val | Trp | Lys | Gly | Leu | Pro | Arg | Glu | Tyr | Val | Ser | Asp | Lys | Arg |  | 560 |
| Cys | Leu | Pro | Cys | His | Pro | Glu | Cys | Gln | Pro | Gln | Asn | Ser | Ser | Glu | Thr | Cys | Phe | Gly | Ser |  | 580 |
| Glu | Ala | Asp | Gln | Cys | Ala | Ala | Cys | Ala | His | Tyr | Lys | Asp | Ser | Ser | Ser | Cys | Val | Ala | Arg |  | 600 |
|     |     |     |     |     |     |     |     |     |     | 610 |     |     |     |     |     |     |     |     |     |  | 620 |
| Cys | Pro | Ser | Gly | Val | Lys | Pro | Asp | Leu | Ser | Tyr | Met | Pro | Ile | Trp | Lys | Tyr | Pro | Asp | Glu |  | 620 |
| Glu | Gly | Ile | Cys | Gln | Pro | Cys | Pro | Ile | Asn | Cys | Thr | His | Ser | Cys | Val | Asp | Leu | Asp | Glu |  | 640 |
| Arg | Gly | Cys | Pro | Ala | Glu | Gln | Arg | Ala | Ser | Pro | Val | Thr | Phe |     |     |     |     |     |     |  | 654 |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| ATG | GAG | CTG | GCG | GCC | TTG | TGC | CGC | TGG | GGG | CTC | CTC | CTC | GCC | CTC | TTG | 48  |
| Met | Glu | Leu | Ala | Ala | Leu | Cys | Arg | Trp | Gly | Leu | Leu | Leu | Ala | Leu | Leu |     |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| CCC | CCC | GGA | GCC | GCG | AGC | ACC | CAA | GTG | TGC | ACC | GGC | ACA | GAC | ATG | AAG | 96  |
| Pro | Pro | Gly | Ala | Ala | Ser | Thr | Gln | Val | Cys | Thr | Gly | Thr | Asp | Met | Lys |     |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| CTG | CGG | CTC | CCT | GCC | AGT | CCC | GAG | ACC | CAC | CTG | GAC | ATG | CTC | CGC | CAC | 144 |
| Leu | Arg | Leu | Pro | Ala | Ser | Pro | Glu | Thr | His | Leu | Asp | Met | Leu | Arg | His |     |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| CTC | TAC | CAG | GGC | TGC | CAG | GTG | GTG | CAG | GGA | AAC | CTG | GAA | CTC | ACC | TAC | 192 |
| Leu | Tyr | Gln | Gly | Cys | Gln | Val | Val | Gln | Gly | Asn | Leu | Glu | Leu | Thr | Tyr |     |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| CTG | CCC | ACC | AAT | GCC | AGC | CTG | TCC | TTC | CTG | CAG | GAT | ATC | CAG | GAG | GTG | 240 |
| Leu | Pro | Thr | Asn | Ala | Ser | Leu | Ser | Phe | Leu | Gln | Asp | Ile | Gln | Glu | Val |     |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| CAG | GGC | TAC | GTG | CTC | ATC | GCT | CAC | AAC | CAA | GTG | AGG | CAG | GTC | CCA | CTG | 288 |
| Gln | Gly | Tyr | Val | Leu | Ile | Ala | His | Asn | Gln | Val | Arg | Gln | Val | Pro | Leu |     |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| CAG | AGG | CTG | CGG | ATT | GTG | CGA | GGC | ACC | CAG | CTC | TTT | GAG | GAC | AAC | TAT | 336 |
| Gln | Arg | Leu | Arg | Ile | Val | Arg | Gly | Thr | Gln | Leu | Phe | Glu | Asp | Asn | Tyr |     |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| GCC | CTG | GCC | GTG | CTA | GAC | AAT | GGA | GAC | CCG | CTG | AAC | AAT | ACC | ACC | CCT | 384 |
| Ala | Leu | Ala | Val | Leu | Asp | Asn | Gly | Asp | Pro | Leu | Asn | Asn | Thr | Thr | Pro |     |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |     |



Fig. 15 (SEQ ID NO: 9)

|   |     |
|---|-----|
| GTC ACA GGG GCC TCC CCA GGA GGC CTG CGG GAG CTG CAG CTT CGA AGC | 432 |
| Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser |     |
| 130 135 140   |     |
| CTC ACA GAG ATC TTG AAA GGA GGG GTC TTG ATC CAG CGG AAC CCC CAG | 480 |
| Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln |     |
| 145 150 155 160   |     |
| CTC TGC TAC CAG GAC ACG ATT TTG TGG AAG GAC ATC TTC CAC AAG AAC | 528 |
| Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn |     |
| 165 170 175   |     |
| AAC CAG CTG GCT CTC ACA CTG ATA GAC ACC AAC CGC TCT CGG GCC TGC | 576 |
| Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys |     |
| 180 185 190   |     |
| CAC CCC TGT TCT CCG ATG TGT AAG GGC TCC CGC TGC TGG GGA GAG AGT | 624 |
| His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser |     |
| 195 200 205   |     |
| TCT GAG GAT TGT CAG AGC CTG ACG CGC ACT GTC TGT GCC GGT GGC TGT | 672 |
| Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys |     |
| 210 215 220   |     |
| GCC CGC TGC AAG GGG CCA CTG CCC ACT GAC TGC TGC CAT GAG CAG TGT | 720 |
| Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys |     |
| 225 230 235 240   |     |
| GCT GCC GGC TGC ACG GGC CCC AAG CAC TCT GAC TGC CTG GCC TGC CTC | 768 |
| Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu |     |
| 245 250 255   |     |
| CAC TTC AAC CAC AGT GGC ATC TGT GAG CTG CAC TGC CCA GCC CTG GTC | 816 |
| His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val |     |
| 260 265 270   |     |
| ACC TAC AAC ACA GAC ACG TTT GAG TCC ATG CCC AAT CCC GAG GGC CGG | 864 |
| Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg |     |
| 275 280 285   |     |
| TAT ACA TTC GGC GCC AGC TGT GTG ACT GCC TGT CCC TAC AAC TAC CTT | 912 |
| Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu |     |
| 290 295 300   |     |

106050-924530

Fig. 15 (SEQ ID NO: 9)

|   |      |
|---|------|
| TCT ACG GAC GTG GGA TCC TGC ACC CTC GTC TGC CCC CTG CAC AAC CAA | 960  |
| Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln |      |
| 305 310 315 320   |      |
| GAG GTG ACA GCA GAG GAT GGA ACA CAG CGG TGT GAG AAG TGC AGC AAG | 1008 |
| Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys |      |
| 325 330 335   |      |
| CCC TGT GCC CGA GTG TGC TAT GGT CTG GGC ATG GAG CAC TTG CGA GAG | 1056 |
| Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu |      |
| 340 345 350   |      |
| GTG AGG GCA GTT ACC AGT GCC AAT ATC CAG GAG TTT GCT GGC TGC AAG | 1104 |
| Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys |      |
| 355 360 365   |      |
| AAG ATC TTT GGG AGC CTG GCA TTT CTG CCG GAG AGC TTT GAT GGG GAC | 1152 |
| Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp |      |
| 370 375 380   |      |
| CCA GCC TCC AAC ACT GCC CCG CTC CAG CCA GAG CAG CTC CAA GTG TTT | 1200 |
| Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe |      |
| 385 390 395 400   |      |
| GAG ACT CTG GAA GAG ATC ACA GGT TAC CTA TAC ATC TCA GCA TGG CCG | 1248 |
| Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro |      |
| 405 410 415   |      |
| GAC AGC CTG CCT GAC CTC AGC GTC TTC CAG AAC CTG CAA GTA ATC CGG | 1296 |
| Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg |      |
| 420 425 430   |      |
| GGA CGA ATT CTG CAC AAT GGC GCC TAC TCG CTG ACC CTG CAA GGG CTG | 1344 |
| Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu |      |
| 435 440 445   |      |
| GGC ATC AGC TGG CTG GGG CTG CGC TCA CTG AGG GAA CTG GGC AGT GGA | 1392 |
| Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly |      |
| 450 455 460   |      |
| CTG GCC CTC ATC CAC CAT AAC ACC CAC CTC TGC TTC GTG CAC ACG GTG | 1440 |
| Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val |      |
| 465 470 475 480   |      |

106050:5524500

Fig. 15 (SEQ ID NO: 9)

|   |      |
|---|------|
| ATC CTC ATC AAG CGA CGG CAG CAG AAG ATC CGG AAG TAC ACG ATG CGG<br>Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg<br>675 680 685     | 2064 |
| AGA CTG CTG CAG GAA ACG GAG CTG GTG GAG CCG CTG ACA CCT AGC GGA<br>Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly<br>690 695 700     | 2112 |
| GCG ATG CCC AAC CAG GCG CAG ATG CGG ATC CTG AAA GAG ACG GAG CTG<br>Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu<br>705 710 715 720 | 2160 |
| AGG AAG GTG AAG GTG CTT GGA TCT GGC GCT TTT GGC ACA GTC TAC AAG<br>Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys<br>725 730 735     | 2208 |
| GGC ATC TGG ATC CCT GAT GGG GAG AAT GTG AAA ATT CCA GTG GCC ATC<br>Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile<br>740 745 750     | 2256 |
| AAA GTG TTG AGG GAA AAC ACA TCC CCC AAA GCC AAC AAA GAA ATC TTA<br>Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu<br>755 760 765     | 2304 |
| GAC GAA GCA TAC GTG ATG GCT GGT GTG GGC TCC CCA TAT GTC TCC CGC<br>Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg<br>770 775 780     | 2352 |
| CTT CTG GGC ATC TGC CTG ACA TCC ACG GTG CAG CTG GTG ACA CAG CTT<br>Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu<br>785 790 795 800 | 2400 |
| ATG CCC TAT GGC TGC CTC TTA GAC CAT GTC CGG GAA AAC CGC GGA CGC<br>Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg<br>805 810 815     | 2448 |
| CTG GGC TCC CAG GAC CTG CTG AAC TGG TGT ATG CAG ATT GCC AAG GGG<br>Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly<br>820 825 830     | 2496 |
| ATG AGC TAC CTG GAG GAT GTG CGG CTC GTA CAC AGG GAC TTG GCC GCT<br>Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala<br>835 840 845     | 2544 |

106050-554560

Fig. 15 (SEQ ID NO: 9)

|   |      |
|---|------|
| CGG AAC GTG CTG GTC AAG AGT CCC AAC CAT GTC AAA ATT ACA GAC TTC | 2592 |
| Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe |      |
| 850 855 860   |      |
| GGG CTG GCT CGG CTG CTG GAC ATT GAC GAG ACA GAG TAC CAT GCA GAT | 2640 |
| Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp |      |
| 865 870 875 880   |      |
| GGG GGC AAG GTG CCC ATC AAG TGG ATG GCG CTG GAG TCC ATT CTC CGC | 2688 |
| Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg |      |
| 885 890 895   |      |
| CGG CGG TTC ACC CAC CAG AGT GAT GTG TGG AGT TAT GGT GTG ACT GTG | 2736 |
| Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val |      |
| 900 905 910   |      |
| TGG GAG CTG ATG ACT TTT GGG GCC AAA CCT TAC GAT GGG ATC CCA GCC | 2784 |
| Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala |      |
| 915 920 925   |      |
| CGG GAG ATC CCT GAC CTG CTG GAA AAG GGG GAG CGG CTG CCC CAG CCC | 2832 |
| Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro |      |
| 930 935 940   |      |
| CCC ATC TGC ACC ATT GAT GTC TAC ATG ATC ATG GTC AAA TGT TGG ATG | 2880 |
| Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met |      |
| 945 950 955 960   |      |
| ATT GAC TCT GAA TGT CGG CCA AGA TTC CGG GAG TTG GTG TCT GAA TTC | 2928 |
| Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe |      |
| 965 970 975   |      |
| TCC CGC ATG GCC AGG GAC CCC CAG CGC TTT GTG GTC ATC CAG AAT GAG | 2976 |
| Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu |      |
| 980 985 990   |      |
| GAC TTG GGC CCA GCC AGT CCC TTG GAC AGC ACC TTC TAC CGC TCA CTG | 3024 |
| Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu |      |
| 995 1000 1005   |      |
| CTG GAG GAC GAT GAC ATG GGG GAC CTG GTG GAT GCT GAG GAG TAT CTG | 3072 |
| Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu |      |
| 1010 1015 1020  |      |

**Fig. 15** (SEQ ID NO: 9)

|   |      |
|---|------|
| GTA CCC CAG CAG GGC TTC TTC TGT CCA GAC CCT GCC CCG GGC GCT GGG | 3120 |
| Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly |      |
| 1025 1030 1035 1040   |      |
| GGC ATG GTC CAC CAC AGG CAC CGC AGC TCA TCT ACC AGG AGT GGC GGT | 3168 |
| Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly |      |
| 1045 1050 1055  |      |
| GGG GAC CTG ACA CTA GGG CTG GAG CCC TCT GAA GAG GAG GCC CCC AGG | 3216 |
| Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu Ala Pro Arg |      |
| 1060 1065 1070  |      |
| TCT CCA CTG GCA CCC TCC GAA GGG GCT GGC TCC GAT GTA TTT GAT GGT | 3264 |
| Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp Gly |      |
| 1075 1080 1085  |      |
| GAC CTG GGA ATG GGG GCA GCC AAG GGG CTG CAA AGC CTC CCC ACA CAT | 3312 |
| Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His |      |
| 1090 1095 1100  |      |
| GAC CCC AGC CCT CTA CAG CGG TAC AGT GAG GAC CCC ACA GTA CCC CTG | 3360 |
| Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu |      |
| 1105 1110 1115 1120   |      |
| CCC TCT GAG ACT GAT GGC TAC GTT GCC CCC CTG ACC TGC AGC CCC CAG | 3408 |
| Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln |      |
| 1125 1130 1135  |      |
| CCT GAA TAT GTG AAC CAG CCA GAT GTT CGG CCC CAG CCC CCT TCG CCC | 3456 |
| Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro |      |
| 1140 1145 1150  |      |
| CGA GAG GGC CCT CTG CCT GCT GCC CGA CCT GCT GGT GCC ACT CTG GAA | 3504 |
| Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu |      |
| 1155 1160 1165  |      |
| AGG CCC AAG ACT CTC TCC CCA GGG AAG AAT GGG GTC GTC AAA GAC GTT | 3552 |
| Arg Pro Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val |      |
| 1170 1175 1180  |      |
| TTT GCC TTT GGG GGT GCC GTG GAG AAC CCC GAG TAC TTG ACA CCC CAG | 3600 |
| Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln |      |
| 1185 1190 1195 1200   |      |

Fig. 15 (SEQ ID NO: 9)

|   |      |
|---|------|
| GGA GGA GCT GCC CCT CAG CCC CAC CCT CCT CCT GCC TTC AGC CCA GCC | 3648 |
| Gly Gly Ala Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala |      |
| 1205 1210 1215  |      |
| TTC GAC AAC CTC TAT TAC TGG GAC CAG GAC CCA CCA GAG CGG GGG GCT | 3696 |
| Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala |      |
| 1220 1225 1230  |      |
| CCA CCC AGC ACC TTC AAA GGG ACA CCT ACG GCA GAG AAC CCA GAG TAC | 3744 |
| Pro Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr |      |
| 1235 1240 1245  |      |
| CTG GGT CTG GAC GTG CCA GTG TGA                                 | 3768 |
| Leu Gly Leu Asp Val Pro Val                                     |      |
| 1250 1255   |      |

008435-0500-9545860







106050-95E45860

# Herceptin Binding by Direct Elisa 10/5/99

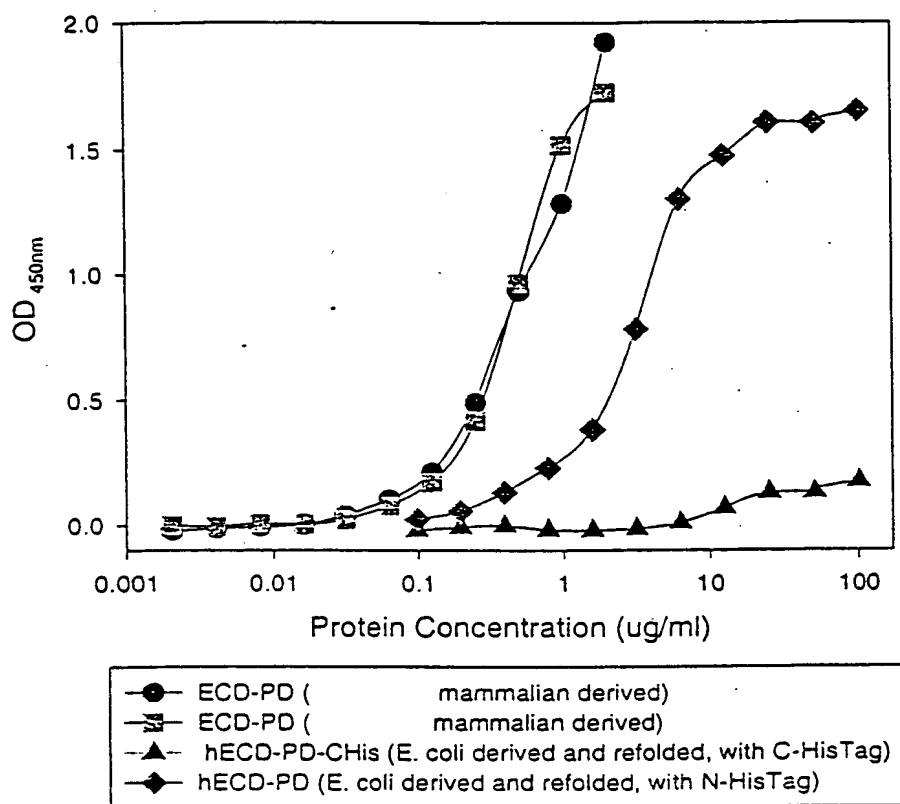
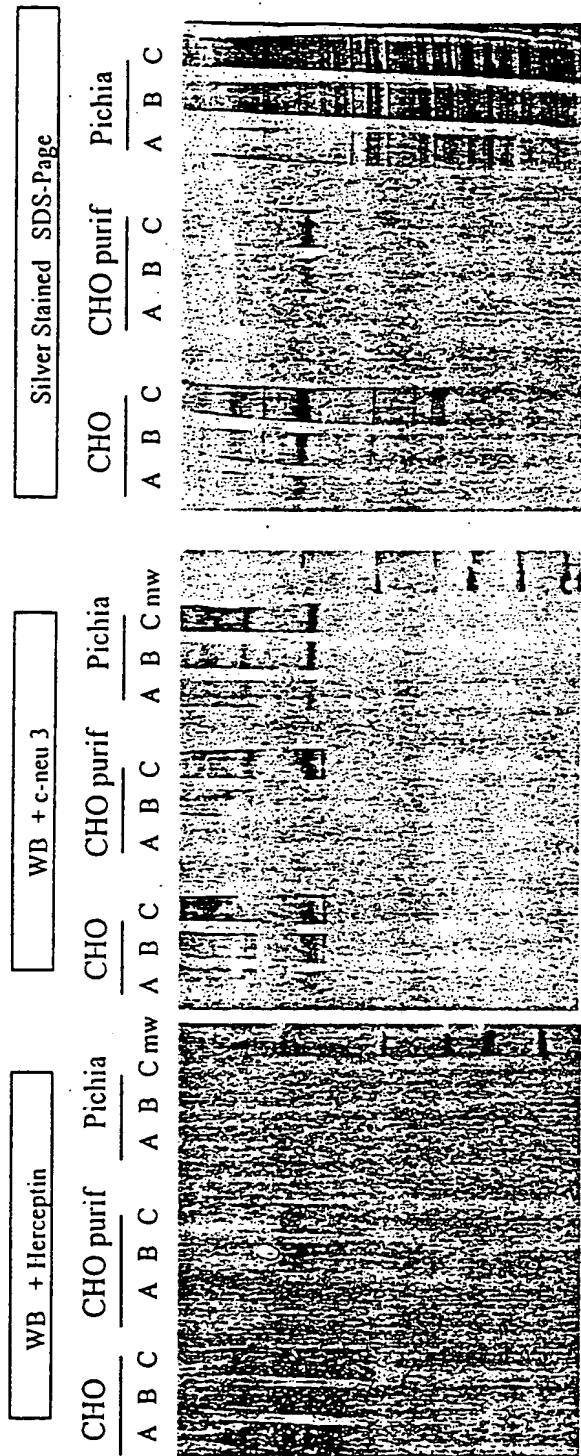


Fig. 17

# Comparison of Her2neu ECD-PD Expression in CHO-K1 (S/SF) and Pichia (Non reducing conditions )



Legend : CHO; A, B, C = 2,5µl / 5µl / 10µl

CHO purif; A, B, C = 125ng / 250ng / 500ng

Pichia ; A, B, C = 2,5µl / 5µl / 10µl from a 1/30 dilution of OD 120

Fig. 19 (SEQ ID NO:11)

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| atggagctgg  | cgccctgggtg | ccgttggggg  | ttcctcctcg  | ccctcctgtc  | ccccggagcc  | 60   |
| gcgggtaccc  | aagtgtgtac  | cggtaccgac  | atgaagtgtc  | gactccctgc  | cagtcctgag  | 120  |
| accacactgg  | acatgcttcg  | ccacctctac  | cagggtgtgc  | aggtgggtgca | gggcaatttg  | 180  |
| gagcttacct  | acctgcccgc  | caatgccagc  | ctctcattcc  | tgcaggacat  | ccaggaagtc  | 240  |
| cagggatata  | tgtcatcgc   | tcacaaccga  | gtgaaacacg  | tcccactgca  | gaggttgccg  | 300  |
| atcgtgagag  | ggactcagct  | ctttgaggac  | aagtatgccc  | tggctgtgct  | agacaaccga  | 360  |
| gacccttttg  | acaacgtcac  | caccgcccgc  | ccaggcagaa  | ccccagaagg  | gctgccccgag | 420  |
| ctgcagcttc  | gaagtctcac  | agagatcttg  | aaggaggag   | ttttgatccg  | tgggaaccct  | 480  |
| cagctctgct  | accaggacat  | ggttttgtgg  | aaggatgtcc  | tccgtaagaa  | taaccagctg  | 540  |
| gctcctgtcg  | acatggacac  | caatcgttcc  | cgggcctgtc  | caccttgtgc  | cccaaccctgc | 600  |
| aaagacaatc  | actgttgagg  | tgagagtcct  | gaagactgtc  | agatcttgac  | tggcaccatc  | 660  |
| tgtactagt   | gctgtgccc   | gtgcaaggcg  | cggctgccc   | ctgactgttg  | ccatgagcag  | 720  |
| tgtgctgcag  | gctgcacggg  | tccaagcat   | tctgactgcc  | tggcctgcct  | ccacttcaat  | 780  |
| catagtggta  | tctgtgagct  | gcactgccc   | gcctcatca   | cctacaacac  | agacaccttc  | 840  |
| gagtccatgc  | tcaaccctga  | gggtcgctac  | acctttgttg  | ccagctgtgt  | gaccacctgc  | 900  |
| ccctacaact  | acctctccac  | ggaagtggga  | tcctgcactc  | tggctgtgtc  | cccgaacaac  | 960  |
| caagaggtca  | cagctgagga  | cggaacacag  | cggtgtgaga  | aatgcagcaa  | gccctgtgct  | 1020 |
| ggagtatgct  | atggtctggg  | catggagcac  | ctccgagggg  | cgagggccat  | caccagtgc   | 1080 |
| aatatccagg  | agtttgctgg  | ctgcaagaag  | atctttggga  | gcctggcatt  | tttgccggag  | 1140 |
| agctttgatg  | ggaacccctc  | ctccggcggt  | gccccactga  | agccagagca  | tctccaagtg  | 1200 |
| ttcgaaacct  | tggaggagat  | cacaggttac  | tatacattt   | cagcatggcc  | agagagcttc  | 1260 |
| caagacctca  | gtgtcttcca  | gaaccttcgg  | gtcattcggg  | gacggattct  | ccatgatggg  | 1320 |
| gcttactcat  | tgacgttgca  | aggcctgggg  | attcactcac  | tggggctacg  | ctcactgcgg  | 1380 |
| gagctgggca  | gtggattggc  | tctcattcac  | cgcaacaccc  | atctctgctt  | tgtaaacact  | 1440 |
| gtaccttggg  | accagctctt  | ccggaacccg  | caccaggccc  | tactccacag  | tgggaaccgg  | 1500 |
| ccagaagagg  | catgtgggtc  | tgaggggctg  | gtctgtaact  | cactgtgtgc  | ccgtggggcac | 1560 |
| tgtgtggggc  | cagggcccac  | ccagtgtgtc  | aactgcagtc  | agtccctccg  | gggccaggag  | 1620 |
| tgtgtggagg  | agtgccgagt  | atggaagggg  | ctccccaggg  | agtatgtgag  | gggcaagcac  | 1680 |
| tgtctgccat  | gccaccccga  | gtgtcagcct  | caaaacagct  | cggagacctg  | ctatggatcg  | 1740 |
| gaggctgacc  | agtgtgaggg  | ttgtgcccac  | tacaaggact  | catcttcctg  | tgtggctcgc  | 1800 |
| tgccccagtg  | gtgtgaagcc  | agacctctcc  | tacatgccta  | tctggaagta  | cccggtatgag | 1860 |
| gagggcatat  | gtcagccatg  | ccccatcaac  | tgcaccact   | catgtgtgga  | cctggacgaa  | 1920 |
| cgaggctgcc  | cagcagagca  | gagagccagc  | ccagtgcacat | tcatcattgc  | aactgtgggtg | 1980 |
| ggcgctcctg  | tgttctctgat | catagtgggtg | gtcattggaa  | tcctaataca  | acgaaggcga  | 2040 |
| cagaagatcc  | ggaagtatac  | catgcgtagg  | ctgctgcagg  | agaccgagct  | gggtggagccg | 2100 |
| ctgacgccc   | gtggagctgt  | gcccacccag  | gctcagatgc  | ggatccctaaa | ggagacagag  | 2160 |
| ctaagggaagc | tgaagggtgct | tgggtcagga  | gccttcggca  | ctgtctacaa  | gggcatctgg  | 2220 |
| atcccagatg  | gggagaacgt  | gaaaatcccc  | gtggccatca  | aggtgttgag  | ggaaaacaca  | 2280 |
| tctcctaaag  | ctaacaaaga  | aatcctagat  | gaagcgtacg  | tcatggctgg  | tgtgggttct  | 2340 |
| ccatatgtgt  | cccgcctcct  | gggcatctgc  | ctgacatcca  | cagtgcagct  | gggtgacacag | 2400 |
| cttatgccct  | atggctgcct  | tctggaccat  | gtccgagaac  | accgaggtcg  | cttaggtctc  | 2460 |
| caggacctgc  | tcaactgggtg | tgttcagatt  | gccaagggga  | tgagctacct  | ggaggaagtt  | 2520 |
| cggtctgttc  | acagggacct  | agctgcccga  | aacgtgctag  | tcaagagtcc  | caaccacgtc  | 2580 |
| aagattaccg  | acttcgggct  | ggcacggctg  | ctggacattg  | atgagactga  | ataccatgca  | 2640 |
| gatgggggca  | aggtgcccac  | caagtggatg  | gcattggaat  | ctattctcag  | acgccggttc  | 2700 |
| actcatcaga  | gtgatgtgtg  | gagctatggg  | gtgactgtgt  | gggagctgat  | gacctttggg  | 2760 |
| gccaaacctt  | acgatgggat  | cccagctcgg  | gagatccctg  | atttgctgga  | gaagggagaa  | 2820 |
| cgctacctc   | agcctccaat  | ctgcaccatc  | gacgtctaca  | tgatcatggg  | caaagtgtgg  | 2880 |
| atgattgact  | ccgaagtctg  | cccagatatt  | cgggagtgtg  | tatcagaatt  | ctcccgtatg  | 2940 |
| gcaagggacc  | cccagcgctt  | tgtggctcat  | cagaacgagg  | acttaggccc  | ctccagcccc  | 3000 |
| atggacagca  | ccttctaccg  | ttcactgctg  | gaggatgatg  | acatggggga  | gctggctgat  | 3060 |
| gctgaagagt  | acctggtacc  | ccagcaggga  | ttcttctccc  | cagacctgc   | cctaggtact  | 3120 |
| gggagcacag  | cccaccgcag  | acaccgcagc  | tcgtcggcca  | ggagtggcgg  | tggtagctg   | 3180 |
| acactgggcc  | tggagccctc  | ggaagaagag  | ccccccagat  | ctccactggc  | tccctccgaa  | 3240 |
| ggggctggct  | ccgatgtgtt  | tgatgggtgac | ctggcagtg   | gggtaaccaa  | aggactgcag  | 3300 |
| agcctctctc  | cacatgacct  | cagccctcta  | cagcgggtaca | gtgaggatcc  | cacattacct  | 3360 |

Fig. 19 (SEQ ID NO:11)

|            |            |            |            |             |            |      |
|------------|------------|------------|------------|-------------|------------|------|
| ctgccccccg | agactgatgg | ctacgttgct | cccctggcct | gcagccccca  | gcccgagtat | 3420 |
| gtgaaccagc | cagagggtcg | gcctcagtct | cccttgaccc | cagaggggtcc | tccgcctccc | 3480 |
| atccgacctg | ctggtgctac | tctagaaaga | cccaagactc | tctctcctgg  | gaaaaatggg | 3540 |
| gttgtcaaag | acgtttttgc | ctttgggggt | gctgtggaga | accctgaata  | cctagcaccc | 3600 |
| agagcaggca | ctgcctctca | gccccaccct | tctcctgcct | tcagcccagc  | ctttgacaac | 3660 |
| ctctattact | gggaccagaa | ctcatcggag | cagggtcctc | caccaagtac  | ctttgaaggg | 3720 |
| acccccactg | cagagaaccc | tgagtaccta | ggcctggatg | tgccagtatg  | a          | 3771 |

098455-0500

Fig. 20 (SEQ ID NO:14)

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Met Glu Leu Ala Ala Trp Cys Arg Trp Gly Phe Leu Leu Ala Leu Leu
 1          5          10          15
Ser Pro Gly Ala Ala Gly Thr Gln Val Cys Thr Gly Thr Asp Met Lys
          20          25          30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
          35          40          45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
          50          55          60
Leu Pro Ala Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65          70          75          80
Gln Gly Tyr Met Leu Ile Ala His Asn Arg Val Lys His Val Pro Leu
          85          90          95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Lys Tyr
          100          105          110
Ala Leu Ala Val Leu Asp Asn Arg Asp Pro Leu Asp Asn Val Thr Thr
          115          120          125
Ala Ala Pro Gly Arg Thr Pro Glu Gly Leu Arg Glu Leu Gln Leu Arg
          130          135          140
Ser Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Arg Gly Asn Pro
145          150          155          160
Gln Leu Cys Tyr Gln Asp Met Val Leu Trp Lys Asp Val Leu Arg Lys
          165          170          175
Asn Asn Gln Leu Ala Pro Val Asp Met Asp Thr Asn Arg Ser Arg Ala
          180          185          190
Cys Pro Pro Cys Ala Pro Thr Cys Lys Asp Asn His Cys Trp Gly Glu
          195          200          205
Ser Pro Glu Asp Cys Gln Ile Leu Thr Gly Thr Ile Cys Thr Ser Gly
          210          215          220
Cys Ala Arg Cys Lys Gly Arg Leu Pro Thr Asp Cys Cys His Glu Gln
225          230          235          240
Cys Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys
          245          250          255
Leu His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu
          260          265          270
Ile Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Leu Asn Pro Glu Gly
          275          280          285
Arg Tyr Thr Phe Gly Ala Ser Cys Val Thr Thr Cys Pro Tyr Asn Tyr
          290          295          300
Leu Ser Thr Glu Val Gly Ser Cys Thr Leu Val Cys Pro Pro Asn Asn
305          310          315          320
Gln Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser
          325          330          335
Lys Pro Cys Ala Gly Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg
          340          345          350
Gly Ala Arg Ala Ile Thr Ser Asp Asn Ile Gln Glu Phe Ala Gly Cys
          355          360          365
Lys Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly
          370          375          380
Asn Pro Ser Ser Gly Val Ala Pro Leu Lys Pro Glu His Leu Gln Val
385          390          395          400
Phe Glu Thr Leu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp
          405          410          415
Pro Glu Ser Phe Gln Asp Leu Ser Val Phe Gln Asn Leu Arg Val Ile

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Fig. 20 (SEQ ID NO:14)

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|
| Asp | Gly | Gly | Lys | Val | Pro | Ile | Lys | Trp | Met | Ala | Leu | Glu | Ser | Ile | Leu | 885  | 890  | 895  |
| Arg | Arg | Arg | Phe | Thr | His | Gln | Ser | Asp | Val | Trp | Ser | Tyr | Gly | Val | Thr | 900  | 905  | 910  |
| Val | Trp | Glu | Leu | Met | Thr | Phe | Gly | Ala | Lys | Pro | Tyr | Asp | Gly | Ile | Pro | 915  | 920  | 925  |
| Ala | Arg | Glu | Ile | Pro | Asp | Leu | Leu | Glu | Lys | Gly | Glu | Arg | Leu | Pro | Gln | 930  | 935  | 940  |
| Pro | Pro | Ile | Cys | Thr | Ile | Asp | Val | Tyr | Met | Ile | Met | Val | Lys | Cys | Trp | 945  | 950  | 955  |
| Met | Ile | Asp | Ser | Glu | Cys | Arg | Pro | Arg | Phe | Arg | Glu | Leu | Val | Ser | Glu | 965  | 970  | 975  |
| Phe | Ser | Arg | Met | Ala | Arg | Asp | Pro | Gln | Arg | Phe | Val | Val | Ile | Gln | Asn | 980  | 985  | 990  |
| Glu | Asp | Leu | Gly | Pro | Ser | Ser | Pro | Met | Asp | Ser | Thr | Phe | Tyr | Arg | Ser | 995  | 1000 | 1005 |
| Leu | Leu | Glu | Asp | Asp | Asp | Met | Gly | Glu | Leu | Val | Asp | Ala | Glu | Glu | Tyr | 1010 | 1015 | 1020 |
| Leu | Val | Pro | Gln | Gln | Gly | Phe | Phe | Ser | Pro | Asp | Pro | Ala | Leu | Gly | Thr | 1025 | 1030 | 1035 |
| Gly | Ser | Thr | Ala | His | Arg | Arg | His | Arg | Ser | Ser | Ser | Ala | Arg | Ser | Gly | 1045 | 1050 | 1055 |
| Gly | Gly | Glu | Leu | Thr | Leu | Gly | Leu | Glu | Pro | Ser | Glu | Glu | Glu | Pro | Pro | 1060 | 1065 | 1070 |
| Arg | Ser | Pro | Leu | Ala | Pro | Ser | Glu | Gly | Ala | Gly | Ser | Asp | Val | Phe | Asp | 1075 | 1080 | 1085 |
| Gly | Asp | Leu | Ala | Val | Gly | Val | Thr | Lys | Gly | Leu | Gln | Ser | Leu | Ser | Pro | 1090 | 1095 | 1100 |
| His | Asp | Leu | Ser | Pro | Leu | Gln | Arg | Tyr | Ser | Glu | Asp | Pro | Thr | Leu | Pro | 1105 | 1110 | 1115 |
| Leu | Pro | Pro | Glu | Thr | Asp | Gly | Tyr | Val | Ala | Pro | Leu | Ala | Cys | Ser | Pro | 1125 | 1130 | 1135 |
| Gln | Pro | Glu | Tyr | Val | Asn | Gln | Pro | Glu | Val | Arg | Pro | Gln | Ser | Pro | Leu | 1140 | 1145 | 1150 |
| Thr | Pro | Glu | Gly | Pro | Pro | Pro | Pro | Ile | Arg | Pro | Ala | Gly | Ala | Thr | Leu | 1155 | 1160 | 1165 |
| Glu | Arg | Pro | Lys | Thr | Leu | Ser | Pro | Gly | Lys | Asn | Gly | Val | Val | Lys | Asp | 1170 | 1175 | 1180 |
| Val | Phe | Ala | Phe | Gly | Gly | Ala | Val | Glu | Asn | Pro | Glu | Tyr | Leu | Ala | Pro | 1185 | 1190 | 1195 |
| Arg | Ala | Gly | Thr | Ala | Ser | Gln | Pro | His | Pro | Ser | Pro | Ala | Phe | Ser | Pro | 1205 | 1210 | 1215 |
| Ala | Phe | Asp | Asn | Leu | Tyr | Tyr | Trp | Asp | Gln | Asn | Ser | Ser | Glu | Gln | Gly | 1220 | 1225 | 1230 |
| Pro | Pro | Pro | Ser | Thr | Phe | Glu | Gly | Thr | Pro | Thr | Ala | Glu | Asn | Pro | Glu | 1235 | 1240 | 1245 |
| Tyr | Leu | Gly | Leu | Asp | Val | Pro | Val |     |     |     |     |     |     |     |     | 1250 | 1255 |      |

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